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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : A61F 2/28, A61L 27/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/45747 (43) International Publication Date: 10 August 2000 (10.08.00)</p>
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<p>(54) Title: BONE-DERIVED IMPLANT FOR LOAD-SUPPORTING APPLICATIONS</p> <div data-bbox="438 1155 1169 1701"></div> <p>(57) Abstract</p> <p>A bone-derived implant (20) is provided which is made up of one or more layers (22, 23) of fully mineralized or partially demineralized cortical bone and, optionally, one or more layers (22, 23) of some other material. The layers (22, 23) constituting the implant (20) are assembled into a unitary structure to provide an implant (20) exhibiting good overall load-supporting properties.</p>		

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Description

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BONE-DERIVED IMPLANT FOR LOAD-SUPPORTING APPLICATIONS

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BACKGROUND OF THE INVENTION**Technical Field**

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The present invention relates to a bone-derived implant fabricated at least in part from strength-imparting cortical bone and intended for use in the repair, replacement and/or augmentation of various portions of animal or human skeletal systems. More particularly, this invention relates to a bone-derived implant which is made up of two or more layers at least one of which is fully mineralized or partially demineralized cortical bone and, optionally, one or more layers fabricated from some other material. The individual layers constituting the implant are assembled into a unitary structure capable of supporting loads.

Description of the Related Art

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The use of autograft bone, allograft bone or xenograft bone is well known in both human and veterinary medicine. See Stevenson et al., *Clinical Orthopedics and Related Research*, 323, pp. 66-74 (1996). In particular, transplanted bone is known to provide support, promote healing, fill bony cavities, separate bony elements such as vertebral bodies, promote fusion and stabilize the sites of fractures. More recently, processed bone has been developed into shapes for use in new surgical applications, or as new materials for implants that were historically made of non-biologically derived materials.

5 U.S. Patent No. 4,678,470 describes a non-layered bone grafting material
produced from bone by a process which includes tanning with glutaraldehyde. The
bone may be pulverized, used as a large block or machined into a precise shape.
10 The tanning stabilizes the material and also renders it non-antigenic. The bone
material may also be demineralized.
5

15 The use of a continuous sheet of demineralized bone or partially
demineralized bone is described in U.S. Patent No. 5,556,430; however, the sheet
must be sufficiently flexible, therefore sacrificing strength, in order to conform to
20 the skeletal site to which it is applied.

10 The surgically implantable sheet described in U.S. Patent No. 5,507,813 is
formed from elongate bone particles, optionally demineralized, containing
25 biocompatible ingredients, adhesives, fillers, plasticizers etc.

U.S. Patent No. 4,932,973 discloses an artificial organic bone matrix with
30 holes or perforations extending into the organic bone matrix. These holes or
perforations are indicated to be centers of cartilage and bone induction following
15 implantation of the bone matrix.

35 U.S. Patent No. 4,394,370 discloses a one-piece sponge-like bone graft
material fabricated from fully demineralized bone powder or micro particulate
bone, and reconstituted collagen. The sponge-like graft is optionally cross-linked
40 with glutaraldehyde.
20

5 Another one-piece porous implant is described in U.S. Patent No.
10 5,683,459. The implant is made up of a biodegradable polymeric macrostructure,
which is structured as an interconnecting open cell meshwork, and a biodegradable
polymeric microstructure composed of chemotactic ground substances such as
15 hyaluronic acid.

SUMMARY OF THE INVENTION

20 The present invention provides a long felt need in the field by providing a
bone-derived implant capable of supporting loads and, in a preferred embodiment,
through its bone healing activity and ability to incorporate medically/surgically
25 10 useful substances at a surgical site to promote and/or accelerate new bone growth.

It is therefore an object of the present invention to provide a bone-derived
30 implant made up of a plurality of superimposed layers, fixed to each other into a
unitary structure, and possessing compression strength characteristics
approximating those of natural bone.

35 15 It is another object of the invention to provide a bone implant possessing a
network of pores, apertures, perforations, channels or spaces which permits and
encourages penetration by endogenous and exogenous bone healing materials and
40 blood supply, and simultaneously provides a means for incorporating one or more
bone healing substances.

20 45 It is yet a further object of the present invention to provide a bone-derived
implant which can be fashioned into a variety of shapes and sizes which are not

5 limited by constraints imposed by the normal anatomical sizes and/or types of
donor bone which are available for the construction of the implant.

10 In keeping with these and other objects of the invention, there is provided a
bone-derived implant which comprises a plurality of superimposed layers
5 assembled into a unitary structure, at least one layer in the structure being a
15 compression-strength imparting layer fabricated from nondemineralized cortical
bone or partially demineralized cortical bone.

20 The bone-derived implant of the present invention possesses a significant
advantage over prior art bone and bone-derived implants in its ability to
10 approximate the mechanical strength characteristics of natural bone and to permit
gradual transfer of load-bearing support therefrom to newly formed bone tissue
25 over time.

Another important advantage of the bone-derived implant herein over prior
30 art implants lies in its ability to function as a carrier for, and effectively
15 incorporate, one or more medically/surgically useful substances that promote new
bone growth and/or accelerate healing.

35 The term "osteogenic" as used herein shall be understood to refer to the
ability of a substance to induce new bone formation via the participation of living
40 cells from within the substance.

20 The term "osteoconductive" as used herein shall be understood to refer to
the ability of a substance or material to provide biologically inert surfaces which
45 are receptive to the growth of new host bone.

5 The term "osteoinductive" as used herein shall be understood to refer to the
ability of a substance to recruit cells from the host which have the potential for
10 repairing bone tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

15 5 Various embodiments are described below with reference to the drawings
wherein:

FIG. 1 is a cross-sectional view of bone from the diaphyseal region which
20 has been sliced longitudinally into several cortical bone layers;

FIG. 2 is an enlarged perspective view of a bone-derived implant of the
10 invention possessing layers of fully mineralized cortical bone alternating with
25 layers of partially and/or fully demineralized cortical bone;

FIG. 3 is a partial view of the human vertebral column showing a dowel-
30 shaped bone-derived implant of the invention installed at an intervertebral site;

FIG. 4 is a view of the human skull showing a bone-derived implant of the
15 invention fashioned as a zygomatic bone replacement;

35 FIG. 5 is an enlarged perspective view of a lattice-like section of bone-
derived implant; and,

40 FIG. 6 is a partial view of the human vertebral column showing installation
of the bone-derived implant of Fig. 5 at an intervertebral site.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The bone-derived implant of the present invention comprises at least two superimposed layers at least one of the layers being a compression strength-imparting layer derived from nondemineralized cortical bone or cortical bone which has been only partially demineralized. When present as a compression strength-imparting layer, a partially demineralized cortical bone layer should exhibit a fairly high percentage of the compression strength of a comparable layer of nondemineralized cortical bone, e.g., preferably at least about 40, more preferably at least about 50 and still more preferably at least about 60 percent of such strength. Layers of partially demineralized cortical bone which exhibit significantly less than about 40 percent of the compression strength of a comparable layer of fully mineralized cortical bone can optionally be utilized in the bone-derived implant but in some capacity other than a load-bearing one. Depending on the thickness of the layers, there can be anywhere from 2 to about 200 layers overall in the bone-derived implant. The bone-derived implant can include layers of varying thicknesses, e.g., the compression strength-imparting layer(s) can be considerably thicker or thinner than any optional layer(s) that may be present. Thicknesses ranging from about 0.5 to about 20, and preferably from about 1.5 to about 15mm can advantageously be used. In general, the number and thickness of the compression-strength imparting layers in a given bone-derived implant will be such as to provide an overall compression strength for the implant of from about 25 to about 250, and preferably from about 100 to about 200 MPa.

5 The sources of cortical bone for the bone-derived implant of this invention
are preferably allogenic but also include xenogenic sources such as bovine and
10 porcine bone. Where partially or fully demineralized cortical bone is utilized,
such bone can be obtained employing known demineralization techniques, e.g.,
5 those employing strong acids such as hydrochloric acid as described in Reddi et
15 al., *Proc. Nat. Acad. Sci.* 69, pp. 1601-5 (1972), herein incorporated by
reference. The extent of demineralization is a function of the strength of the acid
solution, the shape of the bone and the duration of the demineralization treatment.
20 Reference in this regard may be made to Lewandrowski et al., *J. Biomed*
10 *Materials Res*, 31, pp365-372 (1996), also incorporated herein by reference. The
25 use of partially or fully demineralized bone can be beneficial herein since such
substances exhibit greater initial osteogenic and/or osteoinductive activity than
fully mineralized bone.

30 The compression strength-imparting layer(s) of the bone-derived implant
15 can be provided as monolithic sections of bone or as multi-sectional layers built
up from two or more subsections, e.g., joined to each other in edge-to-edge
35 fashion in a manner which is analogous to planking. In this way, relatively large
compression strength-imparting layers can be constructed from smaller bone
40 sections to provide an implant whose overall size is not limited by the size and/or
20 shape of the cortical bone which is available for its construction.

 Assembling the superimposed layers into a strong unitary structure can be
45 accomplished by a variety of means/procedures, e.g., application of known and
conventional biologically compatible adhesives such as the cyanoacrylates; epoxy-

5 based compounds, dental resin sealants, dental resin cements, glass ionomer
cements, polymethyl methacrylate, gelatin-resorcinol-formaldehyde glues,
10 collagen-based glues, inorganic bonding agents such as zinc phosphate, magnesium
phosphate or other phosphate-based cements, zinc carboxylate, etc., and protein-
5 based binders such as fibrin glues and mussel-derived adhesive proteins; the use of
mechanical fasteners such as pins, screws, dowels, etc., which can be fabricated
15 from natural or synthetic materials and bioabsorbable as well as nonbioabsorbable
materials; laser tissue welding; and, ultrasonic bonding. If desired, the layers of
20 the bone-derived implant can be provided with mechanically interengaging
10 features, e.g., tongue-and-groove or mortise-and-tenon elements, to facilitate their
assembly into the final product and/or to fix the layers to each other in a more
25 secured fashion. In addition to its compression strength-imparting fully
mineralized or partially mineralized cortical bone layers, the bone-derived implant
30 of this invention can optionally possess one or more layers formed from one or
15 more other materials. For example, these optional layers can be based on or
include highly or fully demineralized bone, graphite or pyrolytic carbon, a mineral
35 material such as hydroxyapatite, tricalcium phosphate, bioglass or other
bioceramic or natural or synthetic polymers, e.g., bioabsorbable materials such as
starches, polyglycolide, polylactide, glycolide-lactide copolymer, and the like, and
40 20 nonbioabsorbable polymers such as polymethyl methacrylate,
polytetrafluoroethylene, polyurethane, polyethylene and nylon.

5 If desired, the compression strength axis of one or more compression
strength-imparting layers can be offset relative to the compression strength axis of
10 one or more of the other compression strength-imparting layers in an arrangement
much like that of plywood. For example, compression strength axes of alternating
5 compression strength-imparting layers can be offset by up to 90° from the
compression strength axes of the other compression strength-imparting layers in
15 the implant in order to distribute the overall load-supporting capacity of the
implant in mutually transverse directions.

20 Bone-derived implants of any desirable size and/or configuration can be
10 provided, e.g., by machining or other mechanical shaping operations such as
press-molding. Computerized modeling of a specific implant followed by
25 computerized control of the shaping of the implant can be used to provide an
intricately shaped bone-derived implant which is custom-fitted to the intended site
of application with great precision.

15 The bone-derived implant can possess one or more cavities which, if
desired, can communicate with the surface of the implant through pores, apertures,
35 perforations or channels provided for this purpose and ranging in average diameter
from a few microns to several millimeters. Such cavities and their associated
pores, apertures, perforations and channels can be partially or completely filled
40 with one or more medically/surgically useful substances which promote or
20 accelerate new bone growth or bone healing due, e.g., to some osteogenic,
45 osteoconductive and/or osteoconductive effect. Useful substances of this kind

5 which can be incorporated into the bone-derived implant of this invention include,
e.g., collagen, insoluble collagen derivatives, etc., and soluble solids and/or
liquids dissolved therein, e.g., antiviral agents, particularly those effective against
10 HIV and hepatitis; antimicrobials and/or antibiotics such as erythromycin,
5 bacitracin, neomycin, penicillin, polymyxin B, tetracyclines, viomycin,
chloromycetin and streptomycins, cefazolin, ampicillin, azactam, tobramycin,
15 clindamycin and gentamicin, etc.; biocidal/biostatic sugars such as dextroal,
glucose, etc.; amino acids, peptides, vitamins, inorganic elements, co-factors for
protein synthesis; hormones; endocrine tissue or tissue fragments; synthesizers;
20 enzymes such as collagenase, peptidases, oxidases, etc.; polymer cell scaffolds
10 with parenchymal cells; angiogenic drugs and polymeric carriers containing such
drugs; collagen lattices; antigenic agents; cytoskeletal agents; cartilage fragments,
25 living cells such as chondrocytes, bone marrow cells, mesenchymal stem cells,
natural extracts, tissue transplants, bone, demineralized bone powder (or
30 "demineralized bone matrix" as it may also be referred to), autogenous tissues
15 such as blood, serum, soft tissue, bone marrow, etc.; bioadhesives, bone
morphogenic proteins (BMPs), transforming growth factor (TGF-beta), insulin-like
35 growth factor (IGF-1); growth hormones such as somatotropin; bone digestors;
antitumor agents; immuno-suppressants; permeation enhancers, e.g., fatty acid
40 esters such as laurate, myristate and stearate monoesters of polyethylene glycol,
20 enamine derivatives, alpha-keto aldehydes, etc.; and, nucleic acids. These and
45 similar medically/surgically useful substances can be incorporated into the bone-

5 derived implant of this invention or any of its constituent layers during any stage
of the assembly of the implant. Suitable methods of incorporation include coating,
10 immersion saturation, packing, etc. The amounts of medically/surgically useful
substances utilized can vary widely with optimum levels being readily determined
5 in a specific case by routine experimentation.

15 The bone-derived implant herein is intended to be applied at a bone defect
site, e.g., one resulting from injury, defect brought about during the course of
surgery, infection, malignancy or developmental malformation. The bone-derived
20 implant, suitably sized and shaped as required, can be utilized as a graft or
10 replacement in a wide variety of orthopaedic, neurosurgical and oral and
maxillofacial surgical procedures such as the repair of simple and compound
25 fractures and non-unions, external and internal fixations, joint reconstructions such
as arthrodesis, general arthroplasty, cup arthroplasty of the hip, femoral and
30 humeral head replacement, femoral head surface replacement and total joint
15 replacement, repairs of the vertebral column including spinal fusion and internal
fixation, tumor surgery, e.g., deficit filling, discectomy, laminectomy, excision of
35 spinal cord tumors, anterior cervical and thoracic operations, repair of spinal
injuries, scoliosis, lordosis and kyphosis treatments, intermaxillary fixation of
40 fractures, mentoplasty, temporomandibular joint replacement, alveolar ridge
20 augmentation and reconstruction, inlay bone grafts, implant placement and
revision, sinus lifts, etc. Specific bones which can be repaired or replaced with
45 the bone-derived implant herein include the ethmoid, frontal, nasal, occipital,

5 parietal, temporal, mandible, maxilla, zygomatic, cervical vertebra, thoracic
vertebra, lumbar vertebra, sacrum, rib, sternum, clavicle, scapula, humerus,
10 radius, ulna, carpal bones, metacarpal bones, phalanges, ilium, ischium, pubis,
femur, tibia, fibula, patella, calcaneus, tarsal and metatarsal bones.

5 Referring to the drawings, as shown in FIG. 1, the cortical portion of bone
10 taken from the diaphyseal region is cut into cortical bone layers 11 of varying
width by slicing the bone longitudinally. If desired, cortical bone layers 11 can be
15 further cut to uniform size and shape as in bone layers 22 of the implant 20 shown
in FIG. 2.

10 FIG. 2 illustrates a bone-derived implant 20 comprising alternating layers
of fully mineralized cortical bone 22 and partially demineralized cortical bone 23.
25 Alternatively, one or more layers 23 can be made from a material other than
partially demineralized bone such as fully demineralized bone or mineral
substances such as hydroxyapatite. The total thickness of the bone implant will
30 ordinarily be at least about 5, and preferably at least about 10, mm. Bone-derived
implant 20 can be cut, machined, and/or otherwise formed into any other desired
35 shape or dimension for implantation into a body. For example, a substantially
cylindrically shaped bone implant can be made for use as a long bone segment
replacement, e.g., for a femur. To form a cylinder, a substantially square or
40 rectangular bone-derived implant can be shaped on a lathe to the required
20 diameter. A cavity can be formed by removing material with, for example, a
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5 drill, or, alternatively, a cavity can be formed by assembling appropriately
configured layers.

10 As shown in FIG. 3, cylindrical or dowel-shaped bone-derived implant 30
is shown inserted at the intervertebral fibrocartilage site on the anterior side of
5 vertebral column 31.

15 In FIG. 4, zygomatic bone-derived implant 40 is sized and shaped to form
part of the zygomatic arch and part of the interior orbit of skull 41.

20 As shown in the sectional view of FIG. 5, bone-derived implant 50 is built
up from elongate sections 51 of compression strength-imparting fully mineralized
10 or partially demineralized cortical bone of uniform square cross section and
arranged in lattice-wise fashion employing a suitable adhesive, e.g., of the
25 cyanoacrylate variety. Because of the open structure of implant 50 resulting from
the pattern of longitudinal channels 52 and transverse channels 53, the implant
30 permits the vascular penetration or host bone ingrowth therein and/or the diffusion
15 of one or more medically/surgical useful substances therefrom. Vertical channels
in the lattice-like array can, if desired, be partially or completely occupied by
35 appropriately-configured and dimensioned sections 54 fabricated from fully
mineralized or partially demineralized cortical bone as in cortical bone sections 51
40 or from any of the other substances disclosed herein. Fully assembled bone
20 implant 50 is shown installed in intervertebral space 61 of vertebral column 60 of
FIG. 6.

EXAMPLE 1

EXAMPLE 2

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EXAMPLE 3

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A diaphyseal bone segment about 50 mm in length was saw-cut while continuously wetted with water to provide elongate cortical bone sections of uniform, square cross section. The elongate bone sections were then assembled with cyanoacrylate adhesive to provide a lattice-like structure in which layers of spaced-apart bone sections were arranged transversally with respect to each other. A section of bone-derived implant of this type is illustrated in FIG. 5.

Claims

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5 **WHAT IS CLAIMED IS:**

10 1. A bone-derived implant which comprises a plurality of
 superimposed layers assembled into a unitary structure, at least one layer in the
 structure being a compression strength-imparting layer fabricated from
5 nondemineralized cortical bone or partially demineralized cortical bone.

15 2. The bone-derived implant of Claim 1 wherein the partially
 demineralized bone layer exhibits not less than about 40 percent of the
20 compression strength of a comparable layer of fully mineralized bone.

25 3. The bone-derived implant of Claim 1 wherein the partially
10 demineralized bone layer exhibits not less than about 50 percent of the
 compression strength of a comparable layer of fully mineralized bone.

30 4. The bone-derived implant of Claim 1 wherein the partially
 demineralized bone layer exhibits not less than about 60 percent of the
35 compression strength of a comparable layer of fully mineralized bone.

40 15 5. The bone-derived implant of Claim 1 possessing at least two
 compression strength-imparting layers.

- 5 6. The bone-derived implant of Claim 1 possessing a total thickness of
at least about 5 mm.
- 10 7. The bone-derived implant of Claim 1 possessing a total thickness of
at least about 10 mm.
- 15 5 8. The bone-derived implant of Claim 1 possessing a cross section for
at least a portion of its length which is, or approximates, a circle, oval or polygon,
20 the implant optionally possessing a cavity for at least a portion of its length.
- 25 9. The bone-derived implant of Claim 8 wherein pores, apertures,
perforations or channels provide communication between the cavity and the surface
10 of the bone.
- 30 10. The bone-derived implant of Claim 1 configured as a graft.
- 35 11. The bone-derived implant of Claim 1 configured as a replacement
for a bone or section thereof.
- 40 12. The bone-derived implant of Claim 11 configured as an
15 intervertebral insert, a long bone, a cranial bone, a bone of the pelvis, or a bone
45 of the hand or foot or a section of any of the foregoing.

- 5 13. The bone-derived implant of Claim 1 wherein at least one
mechanical strength-imparting layer is provided as a monolithic bone section.
- 10 14. The bone-derived implant of Claim 1 wherein at least one
mechanical strength-imparting layer is provided as a multi-sectional bone section
15 5 wherein subsections of bone constituting the section are joined to each other in
edge-to-edge fashion.
- 20 15. The bone-derived implant of Claim 1 possessing upper and lower
major exposed surfaces, said surfaces being those of compression strength-
25 imparting layers.
- 10 16. The bone-derived implant of Claim 1 possessing at least one layer
30 fabricated in whole or in part from at least one material which is other than
nondemineralized or partially demineralized cortical bone.
- 35 17. The bone-derived implant of Claim 16 wherein the material
facilitates bone healing.
- 40 18. The bone-derived implant of Claim 17 wherein the material
15 possesses osteogenic, osteoconductive and/or osteoinductive activity.
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19. The bone-derived implant of Claim 18 wherein the material is selected from the group consisting of partially demineralized bone, substantially fully demineralized bone, growth factors, bone morphogenic proteins, bone forming cells, precursor cells, genetic material, inorganic compounds and polymers.

20. The bone-derived implant of Claim 1 wherein each strength-imparting layer possesses the same or different average thickness in the range of from about 0.5 mm to about 20 mm.

21. The bone-derived implant of Claim 1 wherein each layer possesses the same or different average thickness in the range of from about 1.5 mm to about 15 mm.

22. The bone-derived implant of Claim 1 wherein the compression strength axes of at least two consecutive compression strength-imparting layers are offset relative to each other.

23. The bone-derived implant of Claim 1 wherein at least two consecutive compression strength-imparting layers are each made up of spaced-apart sections with the compression strength axes of the layers being offset relative

5 to each other in a lattice-like arrangement defining an array of channels in all three dimensions.

10 24. The bone-derived implant of Claim 23 wherein one or more vertical channels in the array is partially or completely occupied by one or more
15 5 appropriately configured and dimensioned sections of material.

20 25. The bone-derived implant of Claim 24 wherein the sections are fully mineralized bone or partially or fully demineralized bone.

25 26. The bone-derived implant of Claim 23 wherein at least one channel
10 contains an osteogenic, osteoconductive and/or osteoinductive material.

30 27. The bone-derived implant of Claim 26 wherein the material is selected from the group consisting of partially demineralized bone powder, substantially fully demineralized bone powder, growth factors, bone morphogenic
35 proteins, bone forming cells or precursor cells, genetic material, and inorganic
15 compounds or polymers.

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5 28. The bone-derived implant of Claim 5 wherein the axis of one or more
compression-strength axis of one or more compression strength-imparting layers is
offset relative to the compression strength axis of one or more of the other
10 compression strength-imparting layers.

15 5 29. The bone-derived implant of Claim 1 having a compression strength
of from about 25 to about 250 MPa.

20 30. The bone-derived implant of Claim 1 having a compression strength
of from about 100 to about 200 MPa.

25 31. The bone-derived implant of Claim 1 possessing from 2 to about
10 200 layers.

30 32. The bone-derived implant of Claim ¹⁶~~47~~ possessing means for
facilitating diffusion of bone healing material.

35 33. The bone-derived implant of Claim 32 wherein the means for
facilitating diffusion of bone healing material constitutes channels defined within
40 one or more layers.
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34. The bone-derived implant of Claim 1 fabricated in whole or in part from allogenic and/or xenogenic cortical bone.

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35. The bone-derived implant of Claim 1 wherein the superimposed layers are assembled with adhesive.

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36. The bone-derived implant of Claim 1 wherein the superimposed layers are assembled with mechanical fasteners.

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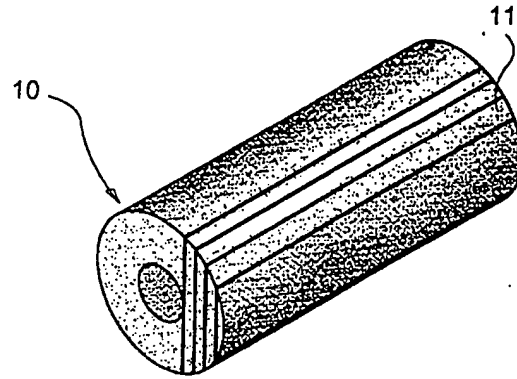


FIG. 1

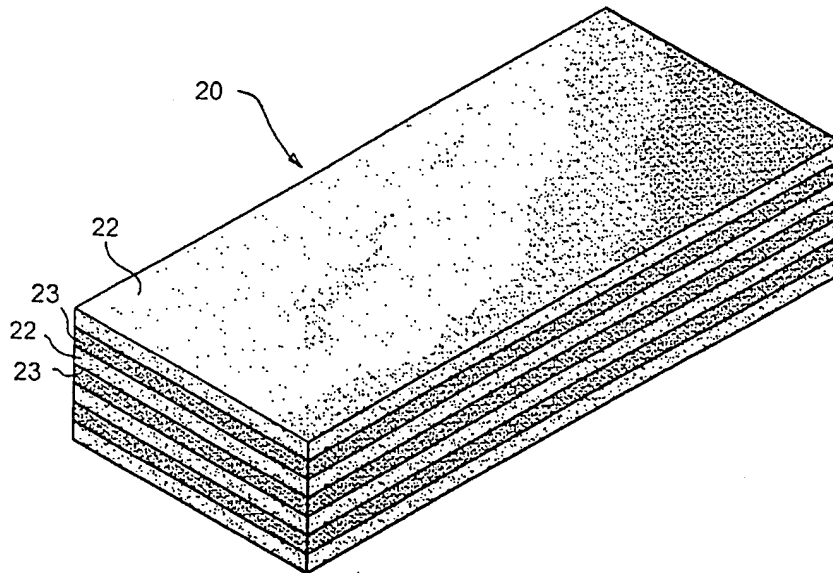


FIG. 2

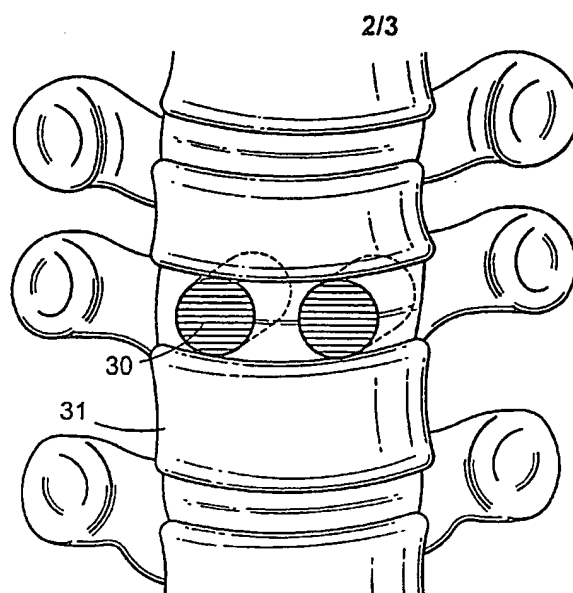


FIG. 3

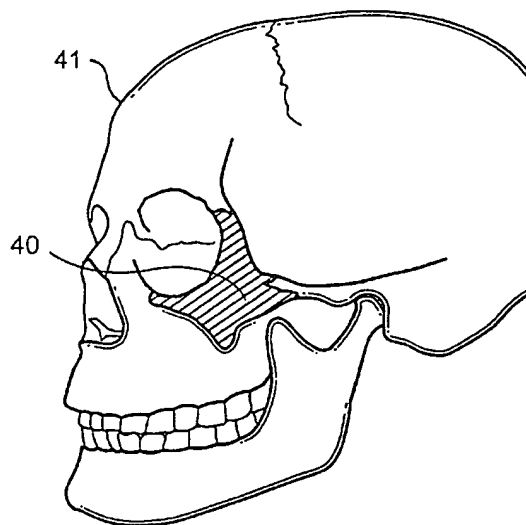


FIG. 4

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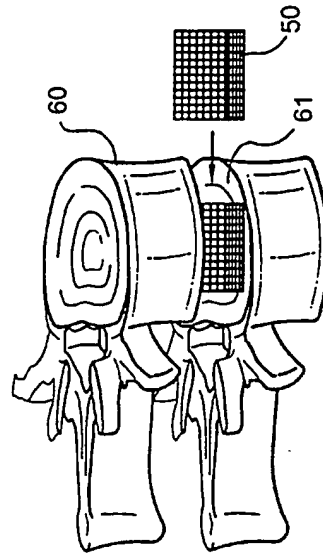


FIG. 6

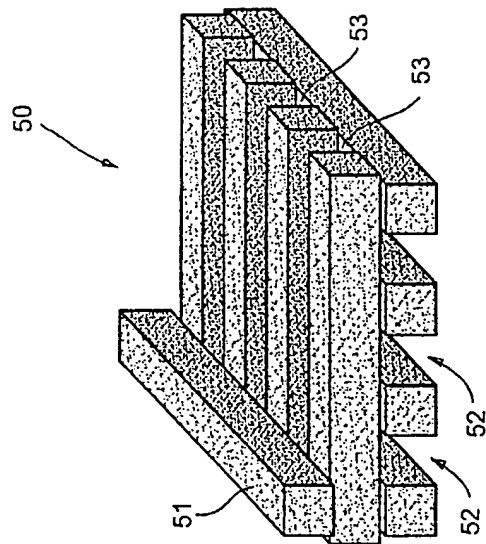


FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 99/02561

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F2/28 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 88 03417 A (MATERIAL CONSULTANTS OY) 19 May 1988 (1988-05-19) page 17, line 29 -page 18, line 4; figures 4,6C,7B, ---	1,5, 8-12,16, 31,34
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 November 1999

Date of mailing of the international search report

10/11/1999

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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